



Review

Anxiety and physiological responses to the Trier Social Stress Test for Children in adolescents with cyclic vomiting syndrome



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ARTICLE INFO

Article history:

Received 1 May 2016

Received in revised form 13 July 2016

Accepted 14 August 2016

Keywords:

Cyclic vomiting syndrome

Child anxiety

Trier Social Stress Test

Salivary cortisol

Alpha amylase

Heart rate variability

ABSTRACT

This study compared anxiety and physiological responses during the Trier Social Stress Test for Children (TSST-C) in adolescents. 38 subjects (26 females) were enrolled: 11 cyclic vomiting syndrome (CVS), 11 anxiety, and 16 controls. Salivary cortisol, α -amylase and heart rate variability (HRV) were assessed during the TSST-C. Anxiety was measured by the Screen for Childhood Anxiety Related Emotional Disorders (SCARED), Anxiety Disorders Interview Schedule, and State-Trait Anxiety Inventory for Children (STAI-C). 11 anxiety and 7 CVS subjects had ≥ 1 anxiety disorder. 82% in the anxiety and CVS groups met criteria for an anxiety disorder on the SCARED. Combining groups, cortisol increased from baseline to recovery during the TSST-C ($p = 0.0004$) and the stressor to recovery ($p = 0.005$). α -amylase did not differ during the TSST-C for the total sample, but increased for anxiety compared to controls from baseline to recovery ($p = 0.01$). HRV decreased during the stressor ($p = 0.0001$) and increased at recovery ($p = 0.004$). No associations were found between biomarkers and trait anxiety. Associations were found between baseline HRV and pre-test state anxiety ($r = -0.406$, $p = 0.012$) and between recovery HRV and post-test state anxiety ($r = -0.501$, $p = 0.002$) for the total sample. Anxiety is prevalent in CVS warranting screening. HRV may serve as a biomarker for evaluating stress as a potential trigger for CVS episodes. State but not trait anxiety was associated with changes in HRV, suggesting acute anxiety may be more relevant in linking stress and CVS episodes.

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Abbreviations: CVS, cyclic vomiting syndrome; EKG, electrocardiogram; HPA, hypothalamic-pituitary-adrenal; HRV, heart rate variability; ICC, intraclass correlation coefficient; RMSSD, root-mean square differences of successive R-R intervals; SCARED, Screen for Childhood Anxiety Related Emotional Disorders; STAI-C, State-Trait Anxiety Inventory for Children; TSST-C, Trier Social Stress Test for Children.

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1. Introduction

Cyclic vomiting syndrome (CVS) is characterized by stereotypic episodes of intense nausea and vomiting, with normal health between episodes. The mechanisms of CVS are not well understood. Several population-based studies estimate the prevalence of pediatric CVS to be approximately 2% (Abu-Arafeh and Russell, 1995; Ertekin et al., 2006). For most youth (82%), CVS is thought to be a migraine variant based on similarities in presentation (i.e., on-off pattern, nausea, abdominal pain, vomiting), response to anti-migraine therapies and family history of migraines (Li et al., 1999; Stickler, 2005; Tarantino et al., 2014). As with migraine, stress is often cited as a trigger for CVS episodes (Li et al., 2008), but it is unclear how the child's stress exposure precipitates a CVS episode.

Youth with CVS have also been found to have a high incidence of anxiety and mood disorders that may impact their ability to cope with stress (Drumm et al., 2012; Forbes et al., 1999; Tarbell and Li, 2008). Children with anxiety disorders are reported to have altered hypothalamic-pituitary-adrenal (HPA) axis and autonomic functioning resembling chronic stress (Dieleman et al., 2015). There is also evidence of altered autonomic function in youth with anxiety disorders (Boyce et al., 2001; Sharma et al., 2011b) and in those with CVS (Chelimsky and Chelimsky, 2007; To et al., 1999).

While clinical reports have shown that stress can trigger a CVS episode, measurement of specific physiological and psychological responses to stress in subjects with CVS in a controlled experimental paradigm has not been studied. The aim of this pilot study was to compare anxiety, changes in hypothalamic-pituitary-adrenal axis (HPA) including salivary cortisol and α -amylase, and autonomic responses during a standardized stress challenge in 3 pediatric groups: subjects with CVS, an anxiety disorder, and healthy controls.

2. Materials and methods

2.1. Participants

Subjects (ages 13–18 years) and their parents were recruited and divided among 3 groups: 1) those who met the international consensus criteria for CVS (Li et al., 2008) were the experimental subjects, 2) those with a diagnosed anxiety disorder (e.g., social phobia, generalized anxiety and/or separation anxiety disorder) as the comparison group, and 3) healthy youth with no major medical or psychiatric illnesses as the controls. We excluded children who were not English speaking or who had other major medical or developmental disorders or psychiatric comorbidity other than anxiety or mood disorders. Participants were recruited from pediatric gastroenterology and pediatric psychiatry clinics, as well as blast emails sent to a university community, an internet posting on the Cyclic Vomiting Syndrome Association website, and flyers

placed in community settings. Interested youth and parents were screened for study eligibility and then scheduled for a clinic visit to obtain informed consent/assent and undergo experimental procedures. Participants received a \$50 stipend for participation. The Institutional Review Board approved this study.

2.2. Measurements

2.2.1. Demographic and medical information

These data were collected during parent or youth interviews and a review of the electronic medical record for participants that were recruited from the hospital's clinical services. Medical record review was used to confirm diagnoses for participants in the CVS and the anxiety groups. Frequency and duration of CVS episodes were obtained for youth with CVS.

2.2.2. Diagnosis of cyclic vomiting syndrome

The diagnostic criteria included: 1) recurrent severe, discrete episodes of vomiting; 2) normal health between episodes; 3) duration of vomiting from hours to days; and 4) no apparent cause of vomiting, as well as supportive criteria that the episodes be stereotypical and self-limited (Li et al., 2008).

2.2.3. Psychiatric diagnoses and psychiatric symptom measures

The child and parent versions of the Anxiety Disorders Interview Schedule for Children (ADIS-C) (Silverman and Albano, 2004) based on the DSM-IV, were used to evaluate all adolescent participants for the presence of anxiety or depressive disorders. Two clinical psychologists conducted the interviews. A subset of the ADIS-C interviews was audiotaped to review for fidelity of administration. Anxiety symptoms were assessed with the Screen for Childhood Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1999). This 41-item questionnaire, validated for use in children 8 years of age and older, is based upon the DSM-IV criteria for anxiety disorders in children. This scale screens for symptoms associated with specific anxiety disorders as well as behaviors such as school avoidance that are common across anxiety disorders in children. Total SCARED scores may range from 0 to 82, with scores 25 or greater indicative of clinically significant anxiety symptoms. Both the child self-report and parent proxy versions of the SCARED were used. The total SCARED scores were used to compare the study groups.

2.2.4. Standardized stress test

The Trier Social Stress Test for Children (TSST-C) (Buske-Kirschbaum et al., 1997) which includes a social stressor (telling a story in front of two neutral judges after 5 min of preparation time) and a cognitive stressor (mental arithmetic-counting backward from 1081 by 7 s) was used to elicit psychological and physiological stress responses in the participants. These two stressors in combination are designed as a

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